AMENDMENTS TO THE DRAWINGS

Please replace Figure 7 with the attached replacement sheet of drawings. Figure 7 has been amended to include specific reference to SEQ ID NO's.

REMARKS

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is being timely filed.

Applicant respectfully requests the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

Claims 1-6 are currently pending in the present application. The Office Action is non-final. Claims 1-6 have been amended without prejudice or disclaimer. No new matter has been added by way of amendment, since each amendment further defines and clarifies each of the structures of the present invention and is supported by the present specification.

Based upon the above considerations, entry of the present amendments are respectfully requested.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraws all rejections and allow the currently pending claims.

Issues Regarding Sequence Rule Compliance – Drawings

As requested by the Examiner, Applicants submit a replacement Figure 7 that is in compliance with Sequence Rules 37 C.F.R. §§ 1.821 through 1.825. No substitute CRF is required since all sequences in Figure 7 were originally present within the filed sequence listing. Figure 7 was only modified to include the SEQ ID identifiers.

Applicants respectfully request reconsideration of the enclosed drawings.

Issues Regarding Information Disclosure Statement

In accordance with the Examiner's request, Applicants enclose copies of the references listed on the International Search Report which were not forwarded to the USPTO by the IB. Specifically, Applicants enclose:

Citation BA (WO-00/04866-A2) and

Citation CA (Parker et al., "Metabolism of 4'-Thio-β-D-arabinofuranosylcytosine", Biochemical Pharmacology, 2000, Vol. 60, pages 1925-1932).

It is noted that the Examiner has considered these references. Now that the references have been submitted, it is believed that this issue has been resolved.

Issues Regarding Priority Document

Applicant desires to obtain benefit of foreign priority under 35 U.S.C. § 119(a)-(d). To this end, enclosed herewith is a verified English translation of the Japanese Patent Application No. 2002-242259 filed in Japan on August 22, 2002. The same provides full 35 USC § 112 support for the invention as instantly claimed. Additionally, the specification has been amended to include this priority information.

Applicants respectfully request consideration of the attached verified English translation.

Rejection Under 35 U.S.C. § 102(a) - Anticipation

Claim 2 stands rejected under 35 U.S.C. § 102(**a**) as anticipated by Minakawa et al. (*Journal of the Chemical Society Perkin Transactions 1,* 2002, 2182-2189, hereinafter "Minakawa et al."). The Examiner asserts that Minakawa et al. teach a compound comprising 4'-thio-cytosine and 5'-triphosphates (page 2182-2185).

In response, Applicants respectfully submit that Minakawa et al. is not prior art to the invention. As evidence of this fact, Applicants submit a verified English translation of the priority document herewith.

Applicants respectfully request reconsideration and subsequent withdrawal of the present rejection.

Rejections Under 35 U.S.C. § 102(b) - Anticipation

Claim 2 stands rejected under 35 U.S.C. § 102(b) as anticipated by Huang et al. (*Chinese Science Bulletin,* 1993, 38:1177-1180, hereinafter "Huang et al."). The Examiner asserts that Huang et al. teach a 4'-thio-2'-deoxythymidine-5'-triphosphate compound and that this compound can be used for antitumor and antiviral agents and for terminating DNA sequencing. Furthermore, claim 2 stands rejected under 35 U.S.C. § 102(b) as anticipated by Chen et al. (U.S. Patent No. 6,004,939, hereinafter "Chen et al."). The Examiner states that Chen et al. teach a 4'-thio-thymidine triphosphate compound (column 24, line 19). Applicants respectfully traverse both rejections.

As the Examiner is aware, the thymidine group of the compounds cited by the Examiner have a thymine group attached at the 2' position. In response to these rejections, Applicants have amended claim 2 without prejudice or disclaimer, to remove thymine from the definition of the base B, thus obviating the above rejections.

Applicants respectfully request reconsideration and subsequent withdrawal of the present rejections.

Rejection Under 35 U.S.C. § 102(e) - Anticipation

Claims 1 and 5 stand rejected under 35 U.S.C. § 102(e) as anticipated by Brown et al. (U.S. Patent Application Publication 2003/0166282, hereinafter "Brown et al."). The Examiner asserts that Brown et al. teach an siRNA oligonucleotide comprising 4'-thio-uridine-triphosphates and teach synthesizing siRNA oligonucleotides by conducting RNA chain elongation reaction via RNA polymerase, for example by PCR. Applicants respectfully traverse.

As the Examiner is aware, the uridine group of the compounds cited by the Examiner have a uracil group attached at the 2' position. In response to these rejections, Applicants have amended claims 1 and 5 without prejudice or disclaimer, to remove uracil from the definition of

the base B, thus making Brown et al. no longer applicable and obviating the above rejections.

Applicants respectfully request reconsideration and subsequent withdrawal of the present rejections.

Rejection Under 35* U.S.C. § 103(a) - *Obviousness

Claims 1-6 stand rejected under 35 U.S.C. § 103(a) as unpatentable over by Brown et al., as applied to claims 1 and 5 above, further in view of Burgess et al. (*Chemical Reviews,* 2000, 100:2047-2059, hereinafter "Burgess et al.") Applicants respectfully traverse the rejection.

Reconsideration and withdrawal of this rejection is respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

A proper obviousness inquiry requires consideration of three factors: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) whether or not the prior art would have taught, motivated, or suggested to those of ordinary skill in the art that they should make the claimed invention (or practice the invention in case of a claimed method or process); and (3) whether the prior art establishes that in making the claimed invention (or practicing the invention in case of a claimed method or process), there would have been a reasonable expectation of success. *See* M.P.E.P. § 2143.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

The teaching, suggestion, motivation test is a valid test for obviousness, but one which cannot be too rigidly applied. *See KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385, 1395 (U.S. 2007). While the courts have adopted a more flexible teaching/suggestion/motivation

(TSM) test in connection with the obviousness standard based on the *KSR v. Teleflex* case which involved a mechanical device in a relatively predictable technological area, it remains true that, despite this altered standard, the courts recognize inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound).

Distinctions Over the Cited Art

Since Applicants amended the claims to remove both uracil and thymidine, Brown et al. does not arrive to the present invention and is no longer is applicable as described above. In addition, the Examiner admits that Brown et al. do not teach a DNA molecule comprising a 4'-thio-deoxynucleosides, nor do they teach a method for synthesizing 4'-thio-deoxynucleosides comprising reacting with pyrophosphoric acid.

However, the Examiner asserts that Burgess et al. teach 28 different methods for nucleoside triphosphate synthesis and teach that no method for preparing nucleoside triphosphates is suitable for all nucleobase derivatives; however, therapeutic applications of nucleoside inhibitors in the art have prompted chemists to explore various venues for efficient triphosphate synthesis procedures (page 2058). As such, the Examiner finds the present invention obvious. Applicants respectfully disagree.

The Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336, quoted with approval in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007).

Burgess et al. describe that nucleoside triphosphates are difficult to make, isolate

characterize and store (*See* Burgess et al., page 2048, section 2 - General Practical Considerations). Also, Burgess et al. indicate that despite the popularity of nucleoside triphosphate syntheses that involve reaction with $POCl_3$, then with pyrophosphate, the method is not perfect and is not successful for all nucleoside derivatives (*Id.* at pg. 2050, column 2, fourth paragraph). Analysis of the reactions also indicates that reaction times are variable and at certain steps the reactions are not perfectly selective to particular intermediates (*Id.*). Additionally, the reactions indicated within Burgess et al, do not involve thio-nucleosides which further complicates whether the reactions are applicable to thio-nucleosides. One in the art would have to perform an undue amount of experimentation since Burgess, et al., do not direct the chemist to thio-nucleoside synthesis, let alone considering thio-nucleoside synthesis for making oligonucleotides more resistant to enzymatic digestion, in light of the present invention.

As noted in *Takeda Chemical Industries,* above, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound. Since the Applicants amended the claims and Brown et al. is specific in the types of nucleosides it covers, a chemist would not be led to modify other thionucleosides and therefore makes Brown et al. inapplicable. There would be no motivation to combine Brown et al. with Burgess et al.

A chemist would not be expected to try all the different syntheses in Burgess et al., especially in light of Burgess et al. indicating that this type of chemistry is very complex and not showing a thio nucleoside reaction. As such, there would be no reasonable expectation for success to do that which Applicants have done based on the cited references.

Since applicants have amended the claims, one skilled in the art would not have arrived to the present invention with the combination of Brown et al. and Burgess et al.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

CONCLUSION

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: October 9, 2007

Respectfully submitted,

By _____ #43505 for
Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicants

Attachment: Fig 7. Replacement
Verified English Translation of Japanese Patent Application No. 2002-242259
WO-00/04866-A2 and
Parker et al., "Metabolism of 4'-Thio-β-D-arabinofuranosylcytosine", Biochemical Pharmacology, 2000, Vol. 60, pages 1925-1932)